Editorial

Raising the bar: the future of EGFR inhibition in non-small lung cancer

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The identification of oncogenic activating mutations in the epidermal growth factor receptor (*EGFR*) and subsequent development of targeted therapies for this subset of non-small cell lung cancer (NSCLC) represents a paradigm shift in solid tumor oncology. If the development and clinical validation of imatinib in chronic myeloid leukemia (CML) cracked open the door of the precision medicine era, then the first-generation EGFR inhibitors swung it wide open. Despite decades of public and private investment in cancer research exemplified by the so-called War on Cancer with the National Cancer Act of 1971, it was not until the early years of the 21st century that patients and physicians alike began to see the kind of transformative change in clinical oncology that could—in some cases, for some patients—turn back the clock of a previously devastating diagnosis.

In the case of NSCLC, the development of targeted therapies for those patients whose tumors harbored an activating mutation in *EGFR* (*EGFR*m NSCLC) led to two major developments that have had a significant influence on other clinical arenas within oncology as well as translational research efforts focused on rational drug design. First, a recognition of the importance of the genomic classification of some tumors, including NSCLC, has led to intense efforts to identify clinically relevant, targetable genomic alterations. In NSCLC alone, within the span of 15 years the list of targetable mutations has grown from *EGFR* to now include rearrangements in *ALK* and *ROS1* as well as mutations in *BRAF*, *MET*, *HER2*, and *RET* (1). Furthermore, in some cases, the landscape of targeted therapies has developed past initial, first-line inhibitors. In a triumph of translational research that has had immediate impact upon the lives of thousands of patients, for some genomic subsets of NSCLC, not only first-line but also second-line or even third-line therapy is now an oral tyrosine kinase inhibitor (TKI) (2-4). In the case of *EGFR*m NSCLC, osimertinib achieved FDA-approval as second-line therapy for patients who progress on first-line EGFR inhibitors after developing the EGFR T790M acquired resistance mutation a mere decade after the T790M mutation was first reported in two patients who progressed on the first-line inhibitor gefitinib (5).

However, in addition to efforts to identify and target additional actionable mutations across NSCLC and other tumor types, the second major development following in the wake of the identification of the *EGFR* mutation has been profound changes in the diagnostic and management strategies of many solid tumors, including NSCLC. Initially, identifying a mutation in an oncogene like *EGFR* was a painstaking process that started as a research test and then became the domain of tertiary referral centers. Once again, just a few years later, the convergence of advancements in both technology and molecular biology have allowed clinical testing for actionable mutations and resistance mutations to become a part of the standard of care around the world.

Indeed, the approval of osimertinib in the second-line setting for *EGFR* mutant NSCLC was specifically linked to the concurrent detection of the EGFR T790M resistance mutation. Ongoing efforts to develop better and faster ways of identifying clinically relevant mutations have even paved the way for the introduction of plasma genotyping as both a clinical and research tool (6).

Against this backdrop of rapid advancement in both clinical therapeutics and diagnostic evaluation, the recent publication of data from The Osimertinib First Time in Patients Ascending Dose (AURA) study (ClinicalTrials.gov identifier: NCT01802632) sets the stage for the future of EGFR targeted therapies in NSCLC (7). As a mutant-selective, covalent inhibitor of the acquired EGFR T790M resistance mutation, osimertinib is currently an approved second-line therapy for *EGFR* patients who develop resistance to first-line EGFR TKIs mediated by the T790M mutation. Previously reported cohorts from the AURA study have shown overall response rates for patients with T790M-mediated acquired resistance ranging from 62–70% with a median PFS ranging from 9.9–12.3 months (8,9). Moreover, when compared to platinum chemotherapy, osimertinib is markedly more effective in this patient cohort, with an ORR of 71% *vs.* 31%, respectively (10).

However, in addition to documented efficacy against the T790M mutation, osimertinib is also an effective inhibitor of baseline EGFR TKI-sensitizing mutations. Moreover, as a mutant-selective inhibitor, osimertinib has an improved side effect profile compared to first-generation (gefitinib, erlotinib) or second-generation (afatinib) EGFR inhibitors currently utilized as first-line therapy. Together, this data raises the intriguing possibility that osimertinib could potentially be an improved therapeutic option for first-line treatment of *EGFR*m NSCLC. Accordingly, as reported in this recent publication in the *JCO*, two cohorts of treatment-naïve patients with locally advanced or metastatic *EGFR*m NSCLC were also enrolled in the AURA study: 30 patients received 80 mg of osimertinib once daily (the currently indicated dose for acquired resistance mediated by T790M) or 160 mg of osimertinib once daily (7). As reported in this recent publication, with a median follow-up of 19.1 months, the ORR in the 80 mg cohort was 67% (95% CI, 47–83%) and 87% in the 160 mg cohort (95% CI, 69–96%). The median PFS was 22.1 months in the 80 mg group (95% CI, 13.7–30.2 months) and 19.3 months in the 160 mg group (95% CI, 13.7–26.0 months) (7). Overall, these results demonstrate a meaningful ORR and prolonged PFS in treatment-naïve *EGFR*m NSCLC and lend support to the ongoing evolution of the best first-line treatment for this group of patients.

Indeed, upon the initial approval of osimertinib in the resistant setting, one obvious direction for future research endeavors centered around this key question: is it better to utilize TKIs sequentially or can outcomes be improved by utilizing a "better" drug first? This publication from the AURA study provides encouraging evidence that osimertinib is not only effective in the first-line setting for *EGFR*m NSCLC but also has a PFS in this context that approaches the sum of the median PFS on a first-line agent (~10 months) and the median PFS on osimertinib in the second line (~10 months). The recently reported results from the randomized FLAURA study (NCT02296125) provide further support for the non-randomized AURA data. In the FLAURA study, patients were randomized to either 80 mg daily of osimertinib or to either 150 mg daily erlotinib or 250 mg daily gefitinib (all doses representing current label indications). The primary endpoint for the FLAURA study was PFS, and at the time of the data cut-off, a consistent PFS benefit was identified in all subgroups of patients receiving osimertinib, with a median PFS of 18.9 months (95% CI, 15.2–21.4 months) compared to 10.2 months (95% CI, 9.6–11.1 months) with standard of care (HR 0.46; 95% CI, 0.37–0.57, P<0.0001) (11). Together, these data suggest that the current standard of care for patients with newly diagnosed advanced *EGFR*m NSCLC is changing, with osimertinib expected to achieve regulatory approval in the first-line setting in the very near future.

However, although the data from the AURA and FLAURA programs is likely to lead to further refinement in the standard of care for *EGFR*m NSCLC patients, there are many unanswered questions that will continue to shape research efforts and future developments. First, the major challenge to the use of targeted therapies in NSCLC and any other context within oncology is the development of acquired resistance. Under the current clinical standard of care in which a first-generation inhibitor is followed by treatment with osimertinib in the context of an acquired T790M mutation, further mutations in EGFR, including the dominant C797S mutation, have been observed to arise in patients treated with osimertinib (12). At present, C797S represents an EGFR mutation without an available targeted inhibitor, although efforts are ongoing to overcome this mechanism of resistance, potentially through the use of an allosteric inhibitor (13). However, when osimertinib is used in the first-line setting, the expected resistance patterns

remain incompletely understood because of the uncertain effects of this new twist on selective pressure. Indeed, when plasma free DNA was evaluated in patients on the AURA cohort of first-line osimertinib, no *EGFR* T790M was detected even though several other putative resistance mechanisms were seen including MET amplification (n=1); *EGFR* and *KRAS* amplification (n=1); *MEK1*, *KRAS*, or *PIK3CA* mutations (n=1 each); *EGFR* C797S mutation (n=2); *JAK2* mutation (n=2); and *HER2* exon 20 insertion mutation (n=1) (7). Together, these findings illustrate the fundamental Achilles heel of the use of targeted therapies in solid tumors: resistance to even the most effective therapy can always emerge. Osimertinib may indeed be a "better" drug by virtue of its improved side effect profile, ability to inhibit a wider range of mutations, and remarkable CNS penetration (14), but even first-line use does not lead to durable, long-term disease control. Unlike the introduction of imatinib for CML and the transition to non-cancer causes of mortality for many of these patients resulting from the durable efficacy of targeted therapies (15), most patients diagnosed today with *EGFR*m NSCLC still have a greater likelihood of dying from their cancer than from anything else. Targeted therapies in this setting have raised the bar, but there is a still a long way to go.

However, it is studies like the first-line AURA cohorts that also suggest possible strategies for improvement. Notably, some of the identified resistance mechanisms in this small cohort are themselves targetable suggesting that a combination therapy approach may provide a way to extend meaningful PFS for many patients. Several clinical trials combining osimertinib and one of a range of other inhibitors are ongoing in the setting of acquired resistance to traditional sequential therapy, including the TATTON study with a range of combination partners (NCT02143466); the BOOSTER study with combination bevacizumab (NCT03133546); combination with a JAK inhibitor (NCT02917993); and combination with a Bcl-2 inhibitor (NCT02520778). Results from these studies may help identify additional resistance pathways and mechanisms that can be exploited in future studies that may combine osimertinib with other agents in the first-line setting.

Notably, one potentially exciting finding that supports a combination approach in the first-line setting is seen in laboratory studies of resistance mechanisms *in vitro* with selective combinations of *EGFR* mutations. In cell lines harboring a baseline *EGFR* activating mutation and artificially engineered to also harbor one of several mutations including C797S that can arise in the context of resistance to osimertinib—but without the presence of the T790M mutation—sensitivity to first-line EGFR TKIs is restored (16). Furthermore, in the context of concurrent treatment with both gefitinib and osimertinib, cell lines with a baseline *EGFR* mutation cannot develop acquired drug resistance even when subjected to chemical mutagenesis (16). On the basis of these findings, a clinical trial utilizing combination gefitinib and osimertinib in the first-line treatment of advanced *EGFR*m NSCLC is ongoing (NCT03122717). It remains to be seen whether combination therapy in this context is clinically feasible (the primary endpoint of this study) and whether or not preliminary data will be obtained to support the possibility of prolonging or even preventing the time to acquired resistance in some patients.

Moving forward, this is both the promise and the challenge of the AURA data and, more broadly, the context of any genomically-defined tumor type with multiple targeted therapy options. Which cohort of patients should receive which therapy or combination of therapies in which order to provide the best quality of life and the most durable long-term response? Are there genomic signatures at diagnosis that can predict a potential mechanism of acquired resistance? What is the best way to monitor patients on a given therapy to identify emerging resistance? When a genomic mechanism of resistance cannot be identified—as happened in the majority of patients on the first-line AURA cohorts—what does this tell us about other mechanisms of resistance and therapeutic alternatives? In a disease like NSCLC that can metastasize to the CNS, is there a specific therapeutic approach that can minimize the likelihood of CNS disease in those patients most at risk? All of these questions remain incompletely answered to date, but they represent the exciting frontier of ongoing translational research efforts in targeted therapies in general and NSCLC in particular. Targeted therapies are not available for all cancer patients, and they are not yet a source of long-term disease control for most solid tumor patients even when a targetable mutation exists. However, the transformative effects of targeted therapies for a subset of cancer patients will continue to represent not only an important benchmark for translational research but also a forum in which ongoing efforts in drug development can continue to advance therapeutic options for as many patients as possible.

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Footnote

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